#### **REMARKS**

## The Invention

The present invention features methods and compositions useful for treating diseases associated with tissue necrosis.

#### The Office Action

Claims 9, 10, 17-25, 32-37, and 41 are pending in this application. All pending claims stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

## Support for Amended Claims

Support for the amendments to claims 9, 10, 24, and 25 can be found in the original claims as filed.

## Rejections Under 35 U.S.C. § 112, first paragraph

Claims 9, 10, 17-25, 32-37, and 41 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner asserts that the specification does not enable a person of ordinary skill in the art to <u>make</u> the claimed <u>derivatives</u> of compound ID# 115807 because the specification does not provide an adequate description of "the steps, reagents, temperatures, pH, etc involved" (Office Action mailed November 5, 2002; page 4). Applicants respectfully traverse this rejection.

As a preliminary matter, applicants point out that the law does not require the specification to teach that which is well known in the art at the time of filing. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987). Specifically, Applicants are permitted to

resort to material outside of the specification in order to satisfy the enablement portion of the statute because in makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention. Atmel Corp. v. Information Storage Devices, Inc., 198

F.3d 1374 (Fed. Cir. 1999). Emphasis added.

In Martin v. Johnson 454 F.2d 746 (C.C.P.A., 1972), the appeals court upheld the ruling of the Board of Patent Interferences who had determined that, without having an enabling synthesis, that the one skilled in the art would know how to make the subject compound merely from knowing its name or structural formula [without] undue experimentation. The conclusion of the court reads as follows:

Although appellants generally appear to agree that a skimpy disclosure can by augmented by showing the skill of the art to have been adequate to fill whatever voids there may be in the written specification, they attempt to draw a distinction between such a case and one, such as they allege we have here, where there is absolutely no how-to-make disclosure. We fail to see on what basis they perceive a difference, but in any event we note that the recognition of the structure of a chemical compound ordinarily provides one skilled in the art with some information as to its synthesis, and the affidavit of record in this case persuades us that that is true here.

In the present circumstances, as in Martin, one skilled in the art would know how to make the subject compounds from publicly available materials upon seeing the formulae. This conclusion is supported by the Declaration of Alexi Degterev, filed with the previous reply, and is discussed further below. Nonetheless, Applicants now bring the Examiner's attention to additional compounds known to those skilled in the art at the time of filing which are within the scope of the claims.

# Representative compounds of claims 9 and 24 were known in the art

Applicants draw the Examiner's attention to compounds [1] - [4] in Figure A below. The compounds are representative species that are within the class of compounds of the instant claims.

## Figure A.

[1]  $R_1$ ,  $R_2$ ,  $R_3$  = H;  $R_4$  = CH<sub>3</sub>; (a) is a double bond, (b) and (c) are single bonds

[2]  $R_1$ ,  $R_2$ ,  $R_3$  = H;  $R_4$  =  $CH_2CH_3$ ; (a) is a double bond, (b) and (c) are single bonds

[3]  $R_1$ ,  $R_2$ ,  $R_3$  = H;  $R_4$  =  $CH_2CH=CH_2$ ; (a) is a double bond, (b) and (c) are single bonds

[4]  $R_1$ ,  $R_3 = H$ ;  $R_3$ ,  $R_4 = CH_3$ ; (b) is a single bond, (a) and (c) are double bonds

These compounds were described in Woo, *J. Korean Agric. Chem Soc.*, 35:132-138, 1992, provided herewith as Exhibit A, Fujiwara, *et al.*, *J. Chemical Soc. Perkin 2*, 1573-77, 1980, provided herewith as Exhibit B, Takahashi, *et al.*, *J. Agric. Food Chem.*, 46:5037-42, 1998, provided herewith as Exhibit C, and Molina, *et al.*, *Tet. Lett.*, 33:4491-94, 1992, provided herewith as Exhibit D, and were prepared utilizing synthetic variations of the "Edman degradation," a well known method in the field of amino and chemistry (see, for example, Edman, Acta Chem. Scand., 4: 283-293, 1950; Waterfield et al., Biochemistry, 9: 832-839, 1970). Edman describes chemical reactions using methyl isothiocyanate to catalyze the formation of a thiohydantoin ring on various amino acid structures. The foregoing examples demonstrate that one skilled in the art, by knowing the structure of a desired compound of the invention, would have recognized the required tryptophan analogs and alkyl isothiocyanates (R-N=C=S), both of which were readily available at the time of filing, required to make the compounds of the invention.

Figure B shows a general synthetic scheme for the preparation of various thiohydantoin analogs of tryptophan that involves the reaction of tryptophan with an isothiocyanate.

Figure B. Preparation of 5-indolylmethyl-2-thiohydantions.

[1] 
$$R = CH_2CH_3$$

[3]  $R = CH_2CH=CH_2$ 

One reference, Woo, describes the synthesis of methylthiohydantion (MTH) amino acid derivatives (Section entitled "Synthesis of Methylthiohydantoins" bridging pages 133 and 134), including tryptophan derivative [1] (Compound ID# 115807), a compound that was also commercially available from ChemBridge and Sigma (Cat. No. M6006) at the time of application filing. The Woo synthesis reacts commercially available amino acids with methylisothiocyanate to produce the MTH amino acid derivates. Further, Woo compares the reaction product with commercially available MTH amino acid standards.

Applicants also provide Fujiwara, et al., which describes preparation of thiohydantoin analogs of amino acids by the Edman procedure for the study of conformation of substituted hydantoins. The general formula of the products provided by this reference (formula [I], Figure C), include compound [2], obtained from tryptophan and ethyl isothiocyanate.

## Figure C.

$$R'$$
 $+$ 
 $NH_2$ 
 $+$ 
 $X = O, S$ 
 $R = Alkyl$ 
 $R' = amino acid side chain$ 

In addition, Takahashi, et al., in the course of investigating the antimutagenic properties of 3,5-disubstituted 2-thiohydantoins, use the cited synthetic methodology to provide a number of thiohydantoin analogs of amino acids (again represented by Formula [I] of Figure C, where X = S), including compound [3] from tryptophan and allyl isothiocyanate.

Examples of tryptophan derivatives (provided with their CAS registry numbers) known at the time of filing for use in making the compounds of the invention include 1-methyl tryptophan [110117-83-4], 4-methyl tryptophan [1954-45-6], 5-methyl tryptophan, 6-methyl tryptophan [2280-85-8], 7-methyl tryptophan [17332-70-6], 5-hydroxy tryptophan [103404-89-3], and 5-methoxy tryptophan [28052-84-8].

In another example, compound [4] of Figure D, a representative compound of claims 9 and 24, where bonds (a) and (c) are double bonds and bond (b) is a single bond, was prepared by Molina, *et al*.

Figure D.

As above for the synthesis of thiohydantoin analogs of tryptophan, this preparation is a general one and one skilled in the art, by knowing the structure of a desired compound of the invention, would have recognized the required 3-carboxy indole analog and alkyl amine (H<sub>2</sub>N-R<sup>2</sup>), both of which were readily available at the time of application, required to make it.

Some examples of indole analogs used in the synthetic scheme of Figure D known at the time of filing include indole-3-carboxaldehyde [487-89-8], 7-methylindole-3-carboxaldehyde [4771-50-0], 5-methoxylindole-3-carboxaldehyde [10601-19-1], 1-methylindole-3-carboxaldehyde [19012-03-4], 1-acetylindole-3-carboxaldehyde [22948-94-], 7-methoxyindole-3-carboxaldehyde, and 5-methylindole-3-carboxaldehyde [52562-50-2]. Enclosed herewith as Exhibit E, are copies of pages of the Sigma catalogue describing these commercially available reagents.

Thus, representative examples of the compounds of the invention existed in the art at the time of application filing. It was nothing more than routine to prepare the additional derivatives, without undue experimentation, as these compounds could be made by one skilled in the art using standard reactions and compounds readily available at that time.

In view of the knowledge of specific compounds and the well recognized routes for the synthesis of the remaining derivatives known in the art at the time the application was filed, Applicants respectfully submit that this rejection should be withdrawn.

# **CONCLUSION**

Applicants submit that the claims are in condition for allowance, and such action is requested. Enclosed is a petition to extend the period for replying for two months, to and including April 5, 2003. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: /////5, 2003

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00742.056003 Reply to FOA mailed 11.5.02